Lead Article

The association between dietary patterns and the novel inflammatory markers platelet-activating factor and lipoprotein-associated phospholipase A_2: a systematic review

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Context: *Atherosclerosis is a disease of chronic inflammation. Recent research has identified 2 novel inflammatory biomarkers: platelet-activating factor (PAF) and lipoprotein-associated phospholipase A_2 (Lp-PLA_2). Diet has been proposed as a mediator of inflammation, but to date, the focus for these novel biomarkers has been on individual foods and nutrients rather than overall dietary patterns.* ***Objective:*** *To systematically review the literature on the association between dietary patterns and PAF and Lp-PLA_2.* ***Data Sources:*** *The PubMed, Embase, CINAHL, and Cochrane CENTRAL literature databases were searched.* ***Data Analysis:*** *Study quality was evaluated using the Quality Criteria Checklist. Sixteen studies ($n = 4$ observational and $n = 12$ interventional) were included and assessed for associations between dietary patterns and PAF and Lp-PLA_2.* ***Conclusion:*** *Study quality varied from neutral ($n = 10$) to positive ($n = 6$). Mediterranean, heart healthy, and vegetarian dietary patterns were associated with improved levels of PAF and Lp-PLA_2. Conversely, Western dietary patterns were less favorable. A range of well-established, healthier dietary patterns may lower inflammation and the risk of atherosclerosis. More well-designed studies are needed to confirm these findings and identify other dietary patterns that improve inflammation.*

INTRODUCTION

Atherosclerosis, the main underlying cause of cardiovascular disease (CVD), is a chronic arterial disease leading to fatty streaks and atheromas in the arterial wall.[1,2] Once thought to be solely caused by dyslipidemia, atherosclerosis is now known to be a result of inflammatory responses.[3] Inflammation is involved in all stages of atherosclerosis, from the initial injury of the endothelium to plaque formation and eventual plaque rupture and thrombosis.[4,5]

Two novel inflammatory markers involved in CVD that are receiving increasing attention are platelet-activating factor (PAF) and lipoprotein-associated phospholipase A_2 (Lp-PLA_2).[6,7] PAF is the most potent lipid inflammatory mediator and is produced upon

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stimulation by numerous cells such as platelets, endothelial cells, and leukocytes.[8,9] PAF is implicated in every step of atherosclerosis (Figure 1).[4,6,10,11] PAF plays a crucial role in the initiation of atherosclerosis and one of its main pro-inflammatory actions is the mediation of adhesion of monocytes to the endothelium and initiation of gene transcription within monocytes to produce inflammatory cytokines such as monocyte chemoattractant protein-1, interleukin (IL) 8, and tumor necrosis factor α (TNF-α).[12,13] PAF also stimulates the release of the proinflammatory cytokine IL-6 from both endothelial cells and monocytes.[14]

PAF induces an influx of Ca^{2+}, which results in increased endothelial permeability as the endothelial cells contract, allowing the migration of low-density lipoprotein (LDL) cholesterol and monocytes into the intima.[15–18] PAF also stimulates reactive oxygen and nitrogen species and contributes to the oxidation of LDL.[6,19] PAF is further involved in the differentiation of monocytes into pro-inflammatory macrophages that engulf oxidized LDL, and is involved in the formation of foam cells and the growth and rupture of plaques.[20,21]

PAF, once produced, triggers an uncontrolled and prolonged inflammatory milieu, because it is responsible for the production of new PAF molecules and additional free radicals.[21,22] Patients with diabetes, heart failure, acute myocardial infarction, and coronary heart disease have elevated levels of PAF.[23–28]

Lp-PLA_2 (alternatively known as platelet-activating factor–acetylhydrolase) is an enzyme that catalyzes hydrolysis of PAF and belongs to the PLA_2 superfamily.[29] As Lp-PLA_2 hydrolyses PAF into the inactive form lyso-PAF, Lp-PLA_2 levels are proposed to be determined by in vivo levels of PAF and may serve as a reliable surrogate marker of PAF.[30] Because Lp-PLA_2 catabolizes PAF, Lp-PLA_2 appears to play an anti-inflammatory role. However, because of its nonspecificity for its ligand, the hydrolysis products of Lp-PLA_2 have been linked to pathologies.[31]

Lp-PLA_2 is primarily secreted by macrophages and circulates in the blood bound to LDL and high-density lipoprotein (HDL), with the majority attached to LDL, and preferentially to small dense fractions.[32] It is proposed that HDL bound to Lp-PLA_2 plays a protective

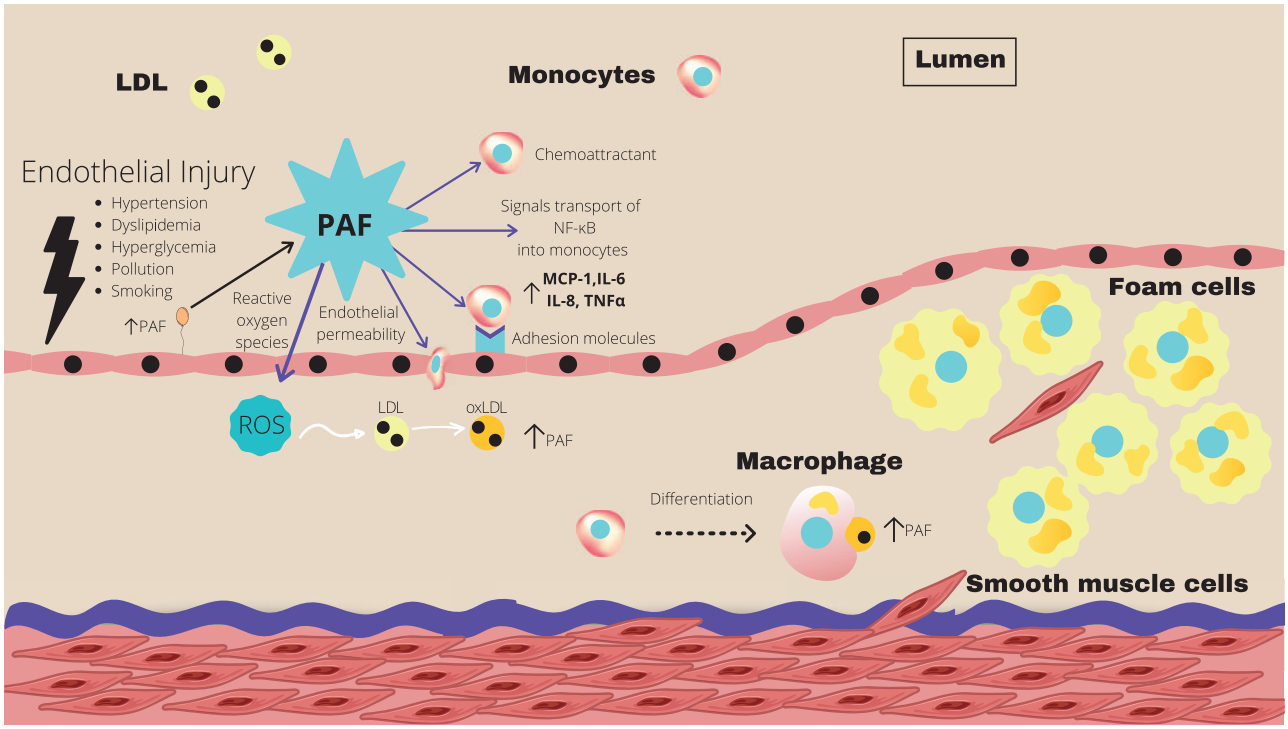

Figure 1 **A simplified schematic of the role PAF plays in the initiation and progression of atherosclerotic plaques**. After exposure to injury, the endothelial cell is activated, triggering the production of PAF and expression of adhesion molecules. PAF acts as a strong chemoattractant and mediates the firm adhesion of monocytes to the endothelium via adhesion molecules. PAF signals the transport of NF-κB into the nucleus of the monocytes, triggering gene transcription of pro-inflammatory cytokines such as MCP-1, IL-6, IL-8, and TNF-α. PAF stimulates the production of ROS, which contributes to the oxidation of LDL. PAF reduces endothelial nitric oxide production and increases endothelial permeability, allowing the transmigration of LDL and monocytes into the intima. PAF is responsible for the differentiation of monocytes into macrophages that engulf oxLDL, which triggers the production of more PAF. *Abbreviations*: IL, interleukin; NF-κB, nuclear factor κB; LDL, low-density lipoprotein; MCP-1, monocyte chemoattractant protein-1; oxLDL, oxidized low-density lipoprotein; PAF, platelet-activating factor; ROS, reactive oxygen species; TNF-α, tumor necrosis factor α.

role, whereas LDL-bound Lp-PLA$_2$ is atherogenic.[32] When associated with LDL, Lp-PLA$_2$ hydrolyzes oxidized phospholipids on the surface of the LDL particles, creating pro-inflammatory and pro-atherogenic by-products such as lysophosphatidylcholine and oxidized, nonesterified fatty acids.[33] Lysophosphatidylcholine and oxidized, nonesterified fatty acids mimic PAF in mediating inflammation by upregulating adhesion molecules; acting as a chemoattractant to monocytes; activating leukocytes; stimulating cytokine production such as IL-6 and TNF-α; contributing to necrosis and apoptosis of macrophages in the plaque; and inducing smooth muscle migration into the intima (Figure 2).[31,34–37] Lp-PLA$_2$ is an independent risk marker for coronary heart disease events, stroke, calcific aortic-valve stenosis, and plaque stability.[38–41]

Previous research on diet and PAF and/or Lp-PLA$_2$ is limited. However, some research has demonstrated that bioactive compounds found in foods regularly consumed in the traditional Mediterranean diet contain natural PAF inhibitors.[20] These compounds inhibit inflammation by preventing PAF from binding to its receptor, blocking the cascade of intracellular signaling and inflammatory processes, and possibly by inhibiting metabolic enzymes used in the remodeling pathway for PAF synthesis.[42–44] This research provides some insight into the potential mechanisms of components within the Mediterranean diet and its established cardioprotective effects.[45]

Research into specific Mediterranean foods that inhibit PAF have predominantly been in vitro studies using washed rabbit platelets and, more recently, human platelets.[46] The foods include fish[47,48]; eggs[49]; honey[50]; wild plants[51]; garden peas[52]; dairy (especially fermented and of goat and sheep origin)[53–56]; goat and sheep meat[57]; flaxseeds[58]; olive oil and olive pomace[59–61]; wine[46]; grapes[62]; *Origanum onites* (Cretan oregano)[63]; clove and cinnamon[64]; onion[65]; garlic[66]; and seeds oils, such as corn, sunflower, and sesame.[59] Foods found outside the Mediterranean region that inhibit PAF include soy sauce,[67] *Camillea sinensis* (tea),[68] and curcumin.[69]

Dietary effects on Lp-PLA$_2$ levels are largely unexplored, but some evidence from studies in humans has shown that low-energy diets with concurrent weight loss can reduce Lp-PLA$_2$ levels, whereas increased energy intake is associated with higher Lp-PLA$_2$ levels.[70,71]

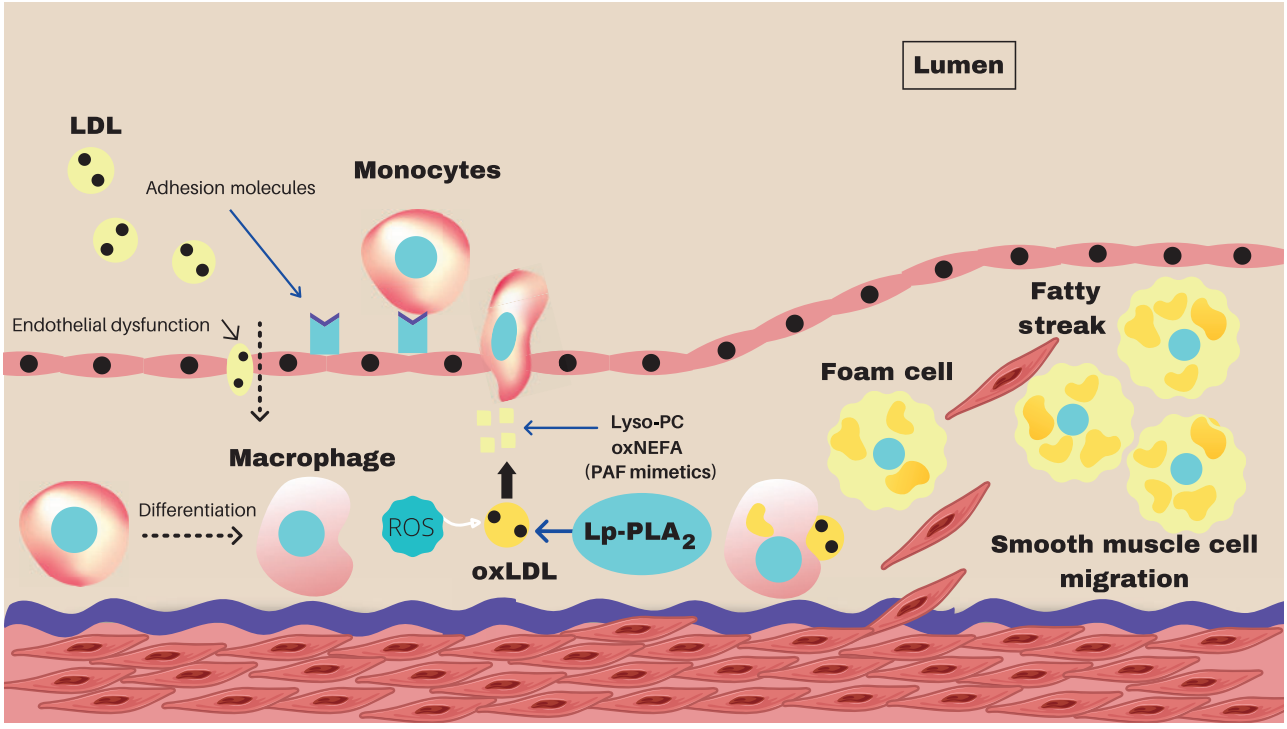

Figure 2 **Lp-PLA$_2$ involvement in the progression of atherosclerosis.** Lp-PLA$_2$ circulates primarily bound to LDL cholesterol, concentrating in small dense LDL. After oxidation of LDL, Lp-PLA$_2$ hydrolyzes oxLDL, creating 2 inflammatory phospholipids, lyso-PC and oxNEFA, both of which mimic PAF. Lyso-PC and oxNEFA upregulate inflammatory mediators such as adhesion molecules, MCP-1, IL-6, and TNF-α; contribute to endothelial dysfunction; promote chemotaxis, drawing monocytes into the arterial intima; trigger smooth muscle cell migration; and induce apoptosis and cytotoxic effects contributing to necrotic core growth. *Abbreviations*: LDL, low-density lipoprotein; Lp-PLA$_2$, lipoprotein-associated phospholipase A$_2$; Lyso-PC, lysophosphatidylcholine; MCP-1, monocyte chemoattractant protein-1; oxLDL, oxidized low-density lipoprotein; oxNEFA, oxidized nonesterified fatty acids; PAF, platelet-activating factor; ROS, reactive oxygen species; TNF-α, tumor necrosis factor alpha.

The replacement of 5% of energy from carbohydrates with energy from protein is associated with a decrease in Lp-PLA_2 activity.[72] An 8-week intervention with the supplementation of omega-3 fatty acids did not influence Lp-PLA_2 activity in older adults,[73] whereas a similar 30-day intervention in people with stable coronary artery disease resulted in decreased Lp-PLA_2 levels.[74]

Studies have varied in terms of the assays used to measure Lp-PLA_2. Lp-PLA_2 assays can measure either plasma concentrations or enzymatic activity. This makes comparisons between studies and interpretation of results difficult. Enzyme activity assays now predominate the recent literature, because mass assays have been shown to be less accurate for risk stratification, because of their ability to only detect a smaller amount of Lp-PLA_2, particularly that associated with HDL.[75,76]

In a recent review considering 17 studies of varying designs that investigated the Mediterranean diet and its components, the authors concluded that this dietary pattern has the potential to lower PAF and Lp-PLA_2 levels.[30] However, the scope of that review was limited to 1 database, and 12 of the 17 included studies examined individual foods, alcohol, or supplements such as fish oil and eicosapentaenoic acid, and not dietary patterns, which are more translatable and relevant across populations. In the present review, we aimed to comprehensively investigate the association between overall dietary patterns and their effect on PAF and Lp-PLA_2 as novel inflammatory biomarkers.

MATERIALS AND METHODS

For this systematic review, we followed the requirements of the Preferred Reporting of Systematic Reviews and Meta-Analyses (PRISMA) statement (Supporting Information online), and the review was registered in July 2021 with the International Prospective Register of Systematic Reviews (PROSPERO no. CRD42020169666; available at http://www.crd.york.ac.uk/PROSPERO).

Search strategy

The databases PubMed, Embase, CINAHL, and Cochrane CENTRAL were searched for relevant studies, with backward citation checking of relevant reviews retrieved in the search. A search for trial protocols through the ClinicalTrials.gov website (www.clinicaltrials.gov) and World Health Organization International Clinical Trials Registry Platform (https://apps.who.int/trialsearch/) was also performed. Databases were searched from inception; the search date was February 21, 2020, with an update to the search performed on February 7, 2021. Table 1 lists PICOS criteria (ie, participants, intervention, comparators, outcomes, and study designs) used to identify studies for inclusion. Eligible studies in any language were considered, provided they were full articles published in a peer-reviewed journal.

A comprehensive search strategy was developed by the research team in conjunction with an experienced librarian. Terms used in the literature search included PAF, platelet-activating factor, Lp-PLA_2, lipoprotein-associated phospholipase A2, diet, and variations of these terms. The complete search strategy is available in the Supporting Information online.

Data management and extraction

Search results were imported into Endnote, version X9.3.3,[77] for de-duplication, then uploaded to Covidence[78] for removal of duplicates and screening. Screening of titles and abstracts against the inclusion criteria was undertaken independently and in duplicate by 2 researchers. Full-text articles were then reviewed independently and in duplicate by 2 researchers and screened for inclusion criteria. Disagreements were resolved by discussion or by a third reviewer.

Data extraction was performed by populating data-extraction tables for multiple study designs from the *Cochrane Handbook for Systematic Reviews of Interventions*,[79] which were further adapted to extract

Table 1 **PICOS criteria for inclusion and exclusion of studies**

Parameter	Inclusion criteria	Exclusion criteria
Participants	Adults $\geq$ 18 y	Aged $<$ 18 y
Intervention	Studies examining diet assessed by dietary patterns, dietary scores, dietary indices, and food patterns	Studies reporting animal or cellular models, or that analyzed consumption of single nutrients or foods rather than a dietary pattern
Comparator	Any/none	Any/none
Outcome	Any measurement of systemic inflammation using PAF and/or Lp-PLA_2. Secondary outcomes included other reported novel markers of inflammation	Other cardiovascular disease outcomes
Study design	Observational (eg, prospective cohort, retrospective cohort, cross sectional, longitudinal, case-control, case series), intervention and randomized controlled trials	None

additional information during this stage. Data extraction was piloted on included articles reporting 3 different study designs, and then was amended to a final format. Data extraction was undertaken by 1 researcher and independently reviewed for accuracy by another researcher.

Data extracted included author, date published, study design, level of evidence, population, sex, country, age, type of dietary pattern, control group, sample size, and study duration. Primary outcomes extracted were PAF levels, PAF-induced platelet aggregation in platelet-rich plasma, specific activities of plasma lyso-PAF and PAF-AH, and LP-PLA_2 mass and activity. Secondary outcomes extracted were any reported biomarkers identified as novel (ie, not recognized as a common inflammatory marker by the research team) and related to CVD. Study authors were contacted by email for additional information if required data had not been published.

Outcomes

The primary outcomes included mean net change in outcome measurements (ie, blood PAF, lyso-PAF, and PAF-AH levels; Lp-PLA_2 mass and/or activity; or platelet aggregation induced by PAF) over the duration of the trial for interventions. Mean net change is the change from baseline to end point in the intervention group minus the change from baseline in the control group, or mean net change between baseline and end point for single-arm studies. Outcomes extracted for observational studies were a comparison of outcome measurements between dietary patterns.

Quality assessment

The quality of included studies was assessed independently and in duplicate using the Academy of Nutrition and Dietetics Quality Criteria Checklist (Table 3).[80] Four relevance questions and 10 quality questions were rated yes or no, ranging from clarity of research question, selection bias, randomization, dropout, blinding, clarity of intervention description, validity of measures, appropriateness of statistical analyses, and conclusions drawn and funding sources. A positive score was determined by "Yes" answers to questions 2, 3, 6, and 7, and at least 1 additional "Yes" on the other questions. If a "No" was the answer to 1 of questions 2, 3, 6, and 7 overall, and there were $\geq$8 "Yes" answers, the study was rated positive. If answers to 2, 3, 6, and 7 were "No," the study was rated as neutral. The study received a negative score if $\geq$6 of the 10 questions were responded to with "No."

Data synthesis

A quantitative synthesis of the data was unable to be performed because of substantial diversity in methodology, dietary patterns, and measurements for outcomes of interest. As such, a narrative review was performed.

Meta-bias(es)

To assess whether reporting bias was present in intervention studies, an investigation of whether each study's protocol had been published before commencement of the trial was undertaken. For all studies published after July 1, 2005, the Clinical Trial Register of the International Clinical Trials Registry Platform of the World Health Organization was searched and outcome reporting bias was assessed on the basis of whether selective reporting of outcomes were present.

RESULTS

Figure 3 presents the process and PRISMA flowchart for study selection. After deduplication, we identified 652 articles through the literature search. After reviewing titles and abstracts, 56 articles were relevant for full-text review. Exclusion of full-text articles was based largely on the lack of examination of a dietary pattern. Sixteen articles were eligible and included for narrative synthesis.

Table 2[17,81–95] lists the characteristics of included studies. The majority of studies were undertaken in Greece (n = 5) and the United States (n = 3). Two studies were undertaken in South Korea and 1 each in Taiwan, India, Sweden, Iran, Spain, and Canada. Specific dietary patterns identified in the literature included "Mediterranean" dietary patterns, "vegetarian" dietary patterns, and "other heart healthy" dietary patterns (which included the Dietary Approaches to Stop Hypertension, or DASH, pattern; Living Heart dietary pattern; National Cholesterol Education Program dietary pattern; and a dietary pattern that replaced refined carbohydrates with whole grains and legumes and more vegetables). A posteriori dietary patterns were also reported and highlighted different patterns consumed across different population groups (namely in Greece, Sweden, and Iran). Data relating to primary and secondary outcomes were extracted from 7 randomized controlled trials (RCTs), 2 non-RCTs, 2 pre-post or single-arm studies, and 1 fixed-sequence intervention trial. The remaining 4 studies were cross-sectional.

In the 4 intervention studies examining Mediterranean dietary patterns, 2 showed significant reductions in PAF-induced aggregation of platelets in both healthy participants and people with type 2

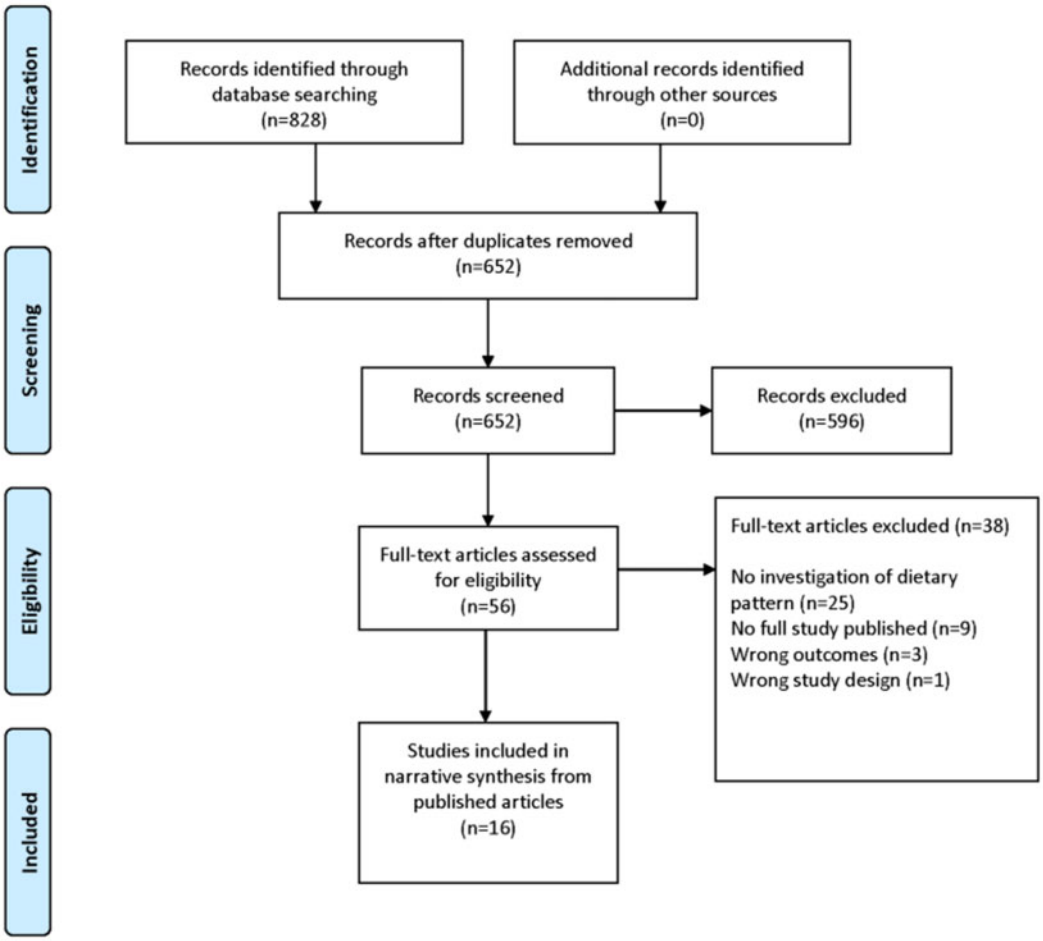

Figure 3 **PRISMA flowchart of article selection.**

diabetes, with the latter showing a much greater response.[17,88] A post hoc study of the Prevención con Dieta Mediterránea trial found a significant favorable change in Lp-PLA_2 activity levels in HDL after a 1-year Mediterranean dietary intervention supplemented with extra-virgin olive oil, when compared with a low-fat diet. However, no significant difference was seen in the Mediterranean diet group supplemented with nuts, when compared with a low-fat diet.[81] The other study was a fixed-sequence study that presented Lp-PLA_2 as percentage change only, which limited the usefulness of the data.[91] In that study, the small number of people whose HDL cholesterol was noted to have increased ($n = 6$ compared with $n = 6$ with reduced HDL), and there was a trend toward a favorable impact on Lp-PLA_2; however, the results were not significant.[91]

Four studies examined vegetarian dietary patterns. One study was an RCT and compared similar Indian vegetarian diets that differed in the addition of either coconut or peanuts.[83] Results showed PAF reduced within the peanut group, but no between-group analysis was conducted.[83] In the single cross-sectional study in Taiwan,[95] Lp-PLA_2 activity was less favorable in omnivores. However, overall, both groups had low average Lp-PLA_2 levels, which could be due to Asian ethnicity.[96] In the 2 papers that reported pre-post single-arm studies, 1 reported significantly lower Lp-PLA_2 levels after 4 weeks of a raw, vegan dietary intervention.[89] The other reported a marginally significant increase in Lp-PLA_2 after 21 days of a largely vegetarian Pritikin dietary pattern.[90]

Heart-healthy dietary patterns were investigated in 5 studies, 4 of which were RCTs. Two of the RCTs focused on the replacement of refined grains with whole grains, increased vegetables, and addition of legumes in a South Korean population sample.[84,85] There were significant reductions in Lp-PLA_2 levels after a 12-week intervention. Another RCT evaluated a 3-week heart-healthy dietary pattern (the Living Heart Diet) combined with exercise and found significant reductions in Lp-PLA_2 compared with participants receiving usual care.[86] A pre-post study with a heart-healthy dietary intervention that was broadly similar to the Living Heart Diet found no significant difference in Lp-PLA_2 levels

Table 2 **Summary of results**

Reference and study location	Study design	Inclusion criteria	Population mean ±SD or (range)	Duration	Dietary pattern/intervention	Control	Outcomes (measurement method) mean ± SD or (range)[a]
Shankar (2017) India[83]	RCT	Healthy adults	n = 58 (31 M, 27 F) Age: 23.8 ± 4.8 y Coconut group weight: 59.8 ± 10.2 kg Peanut group BMI: 56.8 ± 7.3 kg/m^2	90 d	n = 27 Vegetarian dietary pattern with Coconut group: Balanced vegetarian Yogic diet (based on grains, pulses, fruits, and vegetables) + 100 g/d fresh coconut	n = 31 Vegetarian dietary pattern with Peanut group: Balanced vegetarian Yogic diet + 45 g peanuts + 22 g/d peanut oil	*PAF pg/mL (ELISA)* Vegetarian with coconut group: Pre: 186.88 ± 383.11 Post: 194.52 ± 174.40; $P = 0.947$ Vegetarian with peanut group: Pre: 375.25 ± 705.03 **Post: 139.45 ± 144.8; $P = 0.05$** Between-group difference: $P = 0.224$ *PON1 ng/mL* Vegetarian with Coconut group: Pre: 2679.78 ± 878.8 Post: 2755.82 ± 918.3; $P = 0.67$ Vegetarian with peanut group: Pre: 2221.68 ± 647.7 **Post: 2773.59 ± 1145.7; $P = 0.001$** Between-group difference: $P = 0.95$ *MPO ng/mL* Vegetarian with Coconut group: Pre: 657.92 ± 599.22 Post: 677.95 ± 551.65; $P = 0.84$ Vegetarian with Peanut group: Pre: 648.57 ± 529.38 **Post: 924.26 ± 724.24; $P = 0.006$** Between-group difference: $P = 0.17$
Kim et al (2016) South Korea[84]	RCT	Nonobese adults with impaired fasting glucose or newly diagnosed diabetes	n = 80 (M:F ratio: not reported) Age: 40–70 y Weight: not reported BMI: not reported	12 wk	n = 40 Whole-grain dietary pattern Whole-grain diet group: Refined rice replaced with 33% legumes, 33% barley, 33% wild rice 3×/d + 6 servings of vegetables (180–420 g)	n = 40 Usual diet (control) group: Usual Korean diet with refined rice	*Plasma Lp-PLA$_2$ activity (nmol/mL/min) (high-throughput radiometric assay)* Whole-grain diet group: Pre: 28.0 ± 1.2 Post: 25.7 ± 1.11; $P > 0.05$ Usual diet group: Pre: 30.1 ± 1.64 Post: 30.3 ± 1.61; $P > 0.05$ **Between-group difference (change adjusted for baseline): $P < 0.001$** *Unstimulated PBMC Lp-PLA$_2$ activity (nmol/mL/min)* Whole-grain diet group: Pre: 2.16 ± 0.12 **Post: 1.90 ± 0.12; $P < 0.01$** Usual

(continued)

Table 2 **Continued**

Reference and study location	Study design	Inclusion criteria	Population mean ±SD or (range)	Duration	Dietary pattern/intervention	Control	Outcomes (measurement method) mean ± SD or (range)[a]
							diet group: Pre: 2.00 ± 0.12 **Post: 2.28 ± 0.13; $P < 0.01$** **Between-group difference (change adjusted for baseline): $P < 0.001$** *LDL particle size (nm)* Whole-grain diet group: Pre: 24.4 ± 0.15 **Post: 24.6 ± 0.17; $P < 0.001$** Usual diet group: Pre: 24.1 ± 0.12 Post 24.1 ± 0.13; $P > 0.05$ **Between-group difference (change adjusted for baseline): $P = 0.001$**
Kim et al (2014) South Korea[85]	RCT	Adults with impaired fasting glucose, impaired glucose intolerance, or newly diagnosed T2DM	n = 99 (67 M, 32 F) Age, y: Whole-grain group: 56.3 ± 1.2 Usual diet (control) 55.4 ± 1.5 y Weight: not reported BMI (in lieu of weight): Whole-grain diet group: 24.0 ± 0.38 kg/m^2 Usual diet (control): 24.1 ± 0.44 kg/m^2	12 wk	n = 50 Whole-grain dietary pattern Whole-grain diet group: Refined rice replaced with 33% legumes (black soybeans), 33% barley, 33% wild rice 3×/d + 6 servings of vegetables (180–420 g)	n = 49 Usual diet (control) group: Usual Korean diet with refined rice	*Plasma Lp-PLA$_2$ activity (nmol/mL/min) (high-throughput radiometric assay)* Whole-grain diet group: Pre: 30.2 ± 1.32 **Post: 27.8 ± 1.08; $P < 0.01$** Usual diet group: Pre: 29.16 ± 1.29 Post: 29.84 ± 1.28; $P > 0.05$ **Between-group difference (change adjusted for baseline): $P < 0.001$** *Unstimulated PBMC Lp-PLA$_2$ activity (nmol/mL/min)* Whole-grain diet group: Pre: 2.15 ± 0.11 **Post: 1.86 ± 0.11; $P < 0.001$** Usual diet group: Pre: 1.99 ± 0.11 **Post: 2.27 ± 0.13; $P < 0.01$** **Between-group difference (change adjusted for baseline): $P < 0.001$** *LDL particle size (nm)* Whole-grain diet group: Pre: 24.3 ± 0.12 **Post: 24.5 ± 0.14; $P < 0.01$** Usual diet group: Pre: 24.11 ± 0.10 Post: 24.01 ± 0.14; $P > 0.05$ **Between-group difference (change adjusted for baseline): $P = 0.048$**
				24 wk			

(continued)

Table 2 **Continued**

Reference and study location	Study design	Inclusion criteria	Population mean ±SD or (range)	Duration	Dietary pattern/intervention	Control	Outcomes (measurement method) mean ± SD or (range)[a]
Wooten et al (2013) United States[86]	RCT (5-arm drug trial) Data extracted for 2 arms only: (1) Living Heart Diet group (diet and exercise, no medication) and (2) usual care (control) only	Dyslipidemic, HIV-positive adults treated with highly active antiretroviral therapy	n = 107 (98 M, 9 F) Age: 44.8 ± . 9 y Weight: Living Heart Diet 81.6 ± 2.0 kg Usual care (control) 78.4 ± 1.9 kg		n = 22 Heart Healthy dietary pattern, Living Heart Diet group: Carbohydrate, 50% energy; fat, 30% energy (< 7% SFA, 15% MUFA, 8% PUFA, minimal TFA), cholesterol < 200 mg/d, fiber 20–30 g/d + 2 placebos. Aerobic and resistance exercise: 75–90 min 3×/wk.	n = 19 Usual care (control) group: General advice on heart-healthy diet and exercise + 2 placebos. Participants given booklet titled *Nutrition and Your Health*	*Lp-PLA$_2$ mass (ng/mL^1) mean ± SE (ELISA, PLAC test)* Living Heart Diet group: Pre: 387.2 ± 17.9 **Post: 323 ± 27.2; $P < 0.05$** Usual care (control) group Pre: 415.1 ± 31.7 Post: 402.2 ± 25.3; $P > 0.05$ **Between-group difference (adjusted for baseline): $P < 0.05$** *RANTES (ng/mL^1) mean±SE* Living Heart Diet group: Pre: 40.0 ± 3.2 Post: 55.0 ± 11.3; $P > 0.05$ Usual care (control) group: Pre: 42.4 ± 5.9 Post: 50.9 ± 10.4; $P > 0.05$ Between-group difference (adjusted for baseline): $P > 0.05$
Rizos et al (2011) Greece[87]	RCT: only cross-sectional data extracted Results extracted for baseline data only (all 3 arms), after dietary intervention but before randomization to drug interventions	Adults with impaired fasting plasma glucose, mixed dyslipidemia, and stage 1 hypertension	n = 151 (73 M, 78 F) Age: 60 (46–70) y Weight: not reported BMI (in lieu of weight): Group 1: 29 ± 4 kg/m^2 Group 2: 29 ± 5 kg/m^2 Group 3: 28 ± 4 kg/m^2	12 wk	n = 151 DASH dietary pattern: all groups	N/A	***Cross-sectional data extracted*** *Plasma Lp-PLA$_2$ activity (nmol/mL/min) (TCA precipitation)* Group 1 (RT): 57 ± 17 Group 2 (RI): 53 ± 11 Group 3 (RO): 58 ± 14 *Plasma Lp-PLA$_2$ mass (ng/mL) (ELISA, PLAC test)* Group 1: 277 ± 40 Group 2: 301 ± 20 Group 3: 304 ± 34 *Small dense LDL cholesterol (mg/dL) [mmol/L), median (range)]* Group 1: 17 (2–69) [0.4 (0.1–1.8)] Group 2: 15 (7–44) [0.4 (0.2–1.1)] Group 3: 17 (2–78) [0.4 (0.1–2)] *LDL particle size (Å)* Group 1: 261 ± 7 Group 2: 262 ± 4 Group 3: 262 ± 6
Karantonis et al (2005 Greece[88]	Non-RCT	T2DM: managed with diet or OHAs. Healthy age- and weight-matched adults	n = 67 (35 M, 32 F) Age: 56 (26–74) y Weight: 77 ± 9 kg	4 wk	Total n = 45 2 groups: Healthy: n = 22; T2DM: n = 23] Mediterranean-type dietary pattern: Based on fast-food meals pretested for ability to reduce	Total n = 22 (T2DM: all) Usual diet	*PAF EC_{50} (PAF-induced platelet aggregation in PRP)* Healthy group: Pre: 1.45 ± 1.47 **Post: 2.70 ± 2.59; $P = 0.023$** T2DM group: Pre: 1.02 ± 1.38

(continued)

Table 2 **Continued**

Reference and study location	Study design	Inclusion criteria	Population mean ±SD or (range)	Duration	Dietary pattern/intervention	Control	Outcomes (measurement method) mean ± SD or (range)[a]
					PAF-induced aggregation in vitro (TPL)		**Post: 2.40 ± 4.65; *P* = 0.019** Usual/control (T2DM) group: Pre: 0.774 ± 0.522 Post: 0.831 ± 0.5; *P* = 0.285
Roberts et al (2006) USA[90]	Single-arm trial	Overweight or obese adult males	n = 22 (22 M) Age : 62.8 (46–76) y Weight: 103.4 ± 22.9 kg	21 d	n = 22 Vegetarian dietary pattern Low-fat, Pritikin diet ≥5 servings/d whole grains, ≥4 servings/d vegetables ≥3 servings/d fruit. Protein from plant sources, nonfat dairy ≤ 2 servings/d; fish/fowl 85–140 g/wk. Minimal SFA and trans FA intake; no added fats, sugars + 45–60 min walking/d	N/A	*PAF-AH activity (nmol PAF/min/mg protein) (solid-phase chromatography with liquid scintillation)* Pre: 23.4 ± 0.6 **Post: 24.6 ± 0.6; *P* = 0.05** *PON1 activity per mg/HDL* Pre: 669.2 ± 95.6 Post: 684.8 ± 99.7; *P* > 0.05
Observational studies							
Hlebowicz et al (2011) Sweden[94]	Prospective cohort study	Adult men and women No diagnosis of diabetes (IFG eligible) or previous history of CVD	n = 4999 (2040 M; 2959 F) Age: M (46–73) y F (45–73) y Weight: not reported	N/A	n = 4999 A posteriori dietary patterns identified by cluster analysis Six dietary patterns 1. Many foods and drinks 2. Fiber-rich bread 15% of energy from fiber-rich bread 3. Low-fat and high-fiber foods 10.5% of total energy from fruit, 8% from low-fat milk, both high-fat and low-fat meats and sweets 4. White bread 16% of total energy from white bread, other major energy sources were low-fat margarine, both high-fat and low-fat meats and sweets 5. Milk-fat pattern 12% of total energy from butter/rapeseed oil spread, other major energy sources included cheese, whole milk, + some white bread and sweets 6. Sweets and cakes pattern 18% of total energy from sugar, sweets, jam; other major energy sources were cakes, biscuits, and soft drinks	N/A	*General linear model (controlled for age, total energy, season, % body fat, WHR) Lp-PLA$_2$ mass (ng/mL^{1}) (ELISA, PLAC test)* Many foods and drinks pattern (n = 1399): **Male: 287.39 ± 3.76 Female: 258.72 ± 2.65** Fiber-rich bread pattern (n = 460): **Male: 286.51 ± 5.48 Female: 257.15 ± 5.17** Low-fat and high-fiber foods pattern (n = 755): **Male: 284.55 ± 6.97* Female: 250.64 ± 3.26*** White-bread pattern (n = 713): **Male: 291.74 ± 4.22 Female: 263.62 ± 4.40** Milk-fat pattern (n = 638): **Male: 308.03 ± 4.84** Female: 269.25 ± 4.23**** Sweets and cakes pattern (n = 1034): **Male: 296.33 ± 4.17 Female: 265.42 ± 3.19 Male: *P* = .009; Female: *P* = 0.004** *Lp-PLA$_2$ activity (ng/mL^{1}) (high-throughput*

(continued)

Table 2 **Continued**

Reference and study location	Study design	Inclusion criteria	Population mean ±SD or (range)	Duration	Dietary pattern/intervention	Control	Outcomes (measurement method) mean ± SD or (range)[a]
							radiom etric assay) Many foods and drinks pattern (n = 1399): Male: 49.17 ± 0.61 **Female: 41.59 ± 0.42*** Fiber-rich bread pattern (n = 460): Male: 50.70 ± 0.89 (lowest association) **Female: 42.98 ± 0.82** Low-fat and high-fiber foods pattern (n = 755): Male: 47.58 ± 1.13 (highest association) **Female: 42.01 ± 0.52** White-bread pattern (n = 713): Male: 49.89 ± 0.68 **Female: 44.06 ± 0.70** (highest association) Milk-fat pattern (n = 638): Male: 50.09 ± 0.78 **Female: 43.27 ± 0.67** Sweets and cakes pattern (n = 1034): Male: 49.93 ± 0.67 **Female: 43.40 ± 0.51** Male: $P = .291$ **Female: $P = 0.007$**
Chen et al (2011) Taiwan[95]	Cross-sectional	Healthy, adult, non-smoking women	n = 363 (363 F) Age: 51.9 ± 9.9 y Weight: not reported BMI (in lieu of weight): Omnivores: 23.28 ± 3.47 kg/m^2 Vegetarians: 22.87 ± 2.94 kg/m^2	N/A	n = 173 Vegetarian dietary pattern Lacto-ovo vegetarian	n = 190 Omnivore dietary pattern	*Lp-PLA$_2$ activity 10^{-3} μmol/min/mL (PAF acetylhydrolase colorimetric assay)* Vegetarian: 18.32 ± 7.19 Omnivore: 20.22 ± 8.13 **Between-group difference: $P < 0.05$** *Univariate linear regression* Vegetarian: $\beta = -0.19$ **(−3.63, 0.016); $P < 0.05$** *Multivariate regression (age and BMI)* Vegetarian: $\beta = -1.79$ **(−3.58, −0.01); $P < 0.05$**
Intervention studies							
Hernaez et al (2020) Spain[81]	RCT	T2DM or ≥ 3 cardiovascular risk factors (cholesterol, hypertension, BMI, smoking, family history)	n = 358 (131 M, 227 F) Age : 66.8 ± 5.8 y Weight: not reported BMI: mean not reported	1 y	Total n = 239 2 groups: Mediterranean diet supplemented with EVOO: n = 120; Mediterranean diet supplemented with nuts: n = 119	Total n = 119 Low-fat diet	PAF-AH activity in HDLs (PAF acetylhydrolase colorimetric assay) (1-y change): Mean change (95%CI) Mediterranean diet with EVOO vs control:

(continued)

Table 2 **Continued**

Reference and study location	Study design	Inclusion criteria	Population mean ±SD or (range)	Duration	Dietary pattern/intervention	Control	Outcomes (measurement method) mean ± SD or (range)[a]
							7.48% (0.17–14.8) Mediterranean diet with nuts vs control: 3.39% (−3.64 to 10.4)
Makariou et al (2019) Greece[82]	RCT Results extracted for single-arm control group only (diet + no supplement)	Adults with metabolic syndrome	n = 50 (25 M, 25 F) Age: 53 (37–67) y Weight: 89.0 ± 13.4 kg	3 mo	n = 25 Heart Healthy Dietary Pattern NCEP ATP III guidelines Fat 25–35% energy (< 7% SFA, reduced TFA), dietary cholesterol < 200 mg/d. Most dietary fat unsaturated; simple sugars limited	N/A	Heart-healthy dietary pattern *Lp-PLA$_2$ activity (nmol/mL/min) (TCA precipitation)* Pre: 57.4 ± 13.3 Post: 52.7 ± 12.4; $P > 0.05$ *sdLDL cholesterol mg/dL* Pre: 7 (0–22) Post: 5 (2–25); $P > 0.05$ *sdLDL proportion, %* Pre: 3.8 ± 2.8 Post: 3.3 ± 2.3; $P > 0.05$ *Mean LDL size (nm)* Pre: 266.5 ± 3.9 Post: 267 ± 3.5; $P > 0.05$
Antonopoulou et al (2006) Greece[17]	Non-RCT	Type 2 diabetes: managed with diet or OHAs. Healthy age- and weight-matched adults	n = 69 (37 M, 32 F) Age: 53 (26–70) y Weight: 77 ± 9 kg	4 wk	Total n = 46 2 groups: Healthy: n = 22; T2DM: n = 24] Mediterranean-type dietary pattern: Based on catering company–supplied meals pretested for ability to reduce PAF aggregation in vitro (TL)	Total n = 23 (T2DM: all) Usual diet	*PAF EC$_{50}$ (PAF-induced platelet aggregation in PRP)* Healthy group: Pre: 1.4 ± 1.4 **Post: 2.70 ± 2.6; $P = 0.023$** T2DM group: Pre: 0.76 ± 0.5 **Post: 4.2 ± 1.2; $P < 0.001$** Baseline significantly different between groups Usual/control (T2DM) group: Pre: 0.77 ± 0.52 Post: 0.83 ± 0.5; $P = 0.285$
Najjar et al (2018) United States[89]	Single-arm trial	Adults with hypertension and dyslipidemia: SBP ≥ 140 mmHg or DBP ≥ 90 mmHg, LDL-C ≥ 100 mg/dL and BMI ≥ 25 kg/m^2.	n = 31 (10 M, 21 F) Age: 53.4 (32–69) y Weight: 108.1 ± 5.1 kg	4 wk	n = 31 Vegetarian dietary pattern (vegan, raw) Vegan, raw plant-based diet: *raw fruits, vegetables, avocado, seeds, and plant foods dehydrated to temperatures ≤ 160°F ad libitum. Cooked foods, animal products, free oils, soda, alcohol, and coffee were excluded.*	N/A	*Lp-PLA$_2$ mass (ng/mL) (not reported)* Vegan raw plant–based diet: Pre: 252.3 ± 136.3 **Post: 210.7 ± 119.1; $P = 0.001$** *MPO (pmol/L)* Pre: 124.1 ± 58.1 Post: 104.5 ± 53.6; $P = 0.056$ *sdLDL cholesterol mg/dL* Pre: 33.7 ± 11.5 **Post: 23.7 ± 8.7; $P < 0.0005$**

(continued)

Table 2 **Continued**

Reference and study location	Study design	Inclusion criteria	Population mean ±SD or (range)	Duration	Dietary pattern/intervention	Control	Outcomes (measurement method) mean ± SD or (range)[a]
Richard et al (2014) Canada[91]	Fixed-sequence intervention	Nonsmoking male adults with metabolic syndrome No CHD or diabetes; not taking lipid-lowering or antihypertensive medication	n = 26 (26 M) Age: 49.4 (24–62) y Weight: 98.3 ± 17.6 kg	10 wk	n = 26 Mediterranean dietary pattern 5-wk controlled feeding intervention: high in whole grains, legumes, fruits, vegetables, fish, olive oil, nuts, and moderate amount of red wine	n = 26 Standard North American diet—the intervention diet followed a 5-wk run-in, which served as the control	*PAF-AH HDL protein* (fold change) *(mass spectrometry iTRAQ)* Med diet vs control = 1.10; $P = 0.845$ error factor = 5.93 (an error factor value > 2 indicates the ratios vary greatly from peptide to peptide)
Seyedi et al (2020) Iran[92]	Cross-sectional	Adult men and women ≥5 of: TC >200 mg/dL, LDL C >100 mg/dL, HDL C <40 mg/dL (M), <50 mg/dL (F), waist circ. = >102 cm (M), >88 cm (F), SBP >140 mmHg, DBP >90 mmHg, antihypertensive medication, age ≥45 y (M), ≥55 y (F), smoker	n = 470 (114 M, 356 F) Age: 40–70 y Weight: not reported	N/A	n = 470 A posteriori dietary pattern identified by factor analysis. Three dietary patterns calculated: 1. Healthy (reference pattern): high in fresh and dried fruits, olives, high-and low-fat dairy products, poultry and fish, liquid oils, and canned products 2. Semi-Mediterranean: characterized by legumes, potatoes, eggs, red meats, tea, and coffee. 3. Western: dominated by carbonated drinks, fast foods, salty snacks, mayonnaise, and organ meats	N/A	*Lp-PLA$_2$ mass ng/mL (ELISA)* Univariate linear regression Western: **β = 0.35 (0.11, 0.78); $P = 0.026$** Semi-Mediterranean: **β = −0.12 (−3.52, −0.16); $P = 0.043$** Multivariate linear regression (age, BMI, activity, EI, FBG, hormone therapy, lipid-lowering drugs) Western: **β = 1.32 (1.05, 1.64); $P = 0.035$** Semi-Mediterranean $\beta = -0.01$ (−0.16, 0.43); $P = 0.75$
Detopoulou et al (2015 Greece[93]	Cross-sectional	Healthy adults No history of CVD or inflammatory disease, no current respiratory infection, dental problems, renal/hepatic abnormalities. Men were age- and BMI-matched to women.	n = 106 (48 M, 58 F) Age : 44 (31–57) y Weight: not reported BMI (in lieu of weight): 27.5 kg/m^2	N/A	Mediterranean Dietary Pattern (and 2 miscellaneous other patterns): 1. A priori MedDietScore (as developed by Panagiotakos et al, 2006): based on nonrefined cereal, fruits, vegetables, potatoes, legumes, olive oil, fish, red meat, poultry, full-fat dairy products, and alcohol). 2. Calculation of dietary antioxidant capacity 3. Six a posteriori dietary patterns identified by principal component analysis 1: Fruits, nuts, and herbal drinks	None	*Total PAF (fmol/mL), median (lower-upper quartile) (PAF-induced platelet aggregation toward washed rabbit platelets)* Male: 82 (29–372) Female: 152 (43–944) Total: 119 (34–578) MedDietScore: Men only (n = 48); Adjusted for age, sex, EI/BMR *Bound PAF* $r = -0.26$; $P = 0.08$ *Total PAF* $r = -0.30$, $P > 0.05$ Dietary antioxidant capacity: *adjusted for age, sex, EI/BMR* *Total PAF (pmol/mL)*

(continued)

Table 2 **Continued**

Reference and study location	Study design	Inclusion criteria	Population mean ±SD or (range)	Duration	Dietary pattern/intervention	Control	Outcomes (measurement method) mean ± SD or (range)[a]
					2: Legumes, vegetables, poultry and fish 3: Low consumption of low-fat dairy, high consumption of full-fat dairy, cheeses, alcohol, and red meat 4: Coffee and low intake of whole-wheat products 5: Refined cereals and full-fat dairy, cheeses 6: Whole-wheat products and olive oil		DAC FRAP: $r = -0.197$; $P = 0.06$ **DAC-TRAP: $r = -0.211$; $P = 0.04$** **DAC TEAC: $r = -0.200$; $P = 0.05$** *Lyso-PAF-AT (nmol/min/mg)* **DAC FRAP: $r = -0.200$; $P = 0.05$** DAC-TRAP: $r = -0.171$; $P = 0.1$ DAC TEAC: $r = -0.146$; $P = 0.1$ *Lp-PLA$_2$ (nmol/min/mL) (TCA precipitation)* DAC FRAP $r = 0.090$; $P = 0.30$ DAC TRAP $r = 0.119$; $P = 0.20$ DAC TEAC $r = 0.110$; $P = 0.30$ *Free PAF, bound PAF, PAF-CPT, and PAF-AH: all results not significant.* A posteriori dietary patterns: *Linear regression adjusted for age, sex, EI/BMR, and other dietary patterns* *Free PAF pmol/mL* Legumes, vegetables, poultry, and fish dietary pattern: -0.157 ± 0.087; $P = 0.07$ *Total PAF pmol/mL* Coffee and low intake of whole-wheat products dietary pattern: -0.147 ± 0.08; $P = 0.06$ *Lyso-PAF-AT (nmol/min/mg)* Fruits, nuts, herbal drinks: -1202 ± 652; $P = 0.06$ Whole-wheat products, olive oil dietary pattern: **-1273 ± 571; $P = 0.02$** *Cox proportional hazards regression (adjusted for age, total energy, season, % body fat, WHR, and smoking)* *Tertile 1: lowest adherence; tertile 3: highest adherence* *Lp-PLA$_2$ mass (ng/mL^1)* Female: Low-fat and high-fiber foods pattern:

(continued)

Table 2 **Continued**

Reference and study location	Study design	Inclusion criteria	Population mean ±SD or (range)	Duration	Dietary pattern/intervention	Control	Outcomes (measurement method) mean ± SD or (range)[a]
							Tertile 2: OR, 0.89 (0.71, 1.12) Tertile 3: OR, 0.69 (0.54, 0.87) $P = 0.002$ Sweets and cakes pattern: Tertile 2: OR, 1.20 (0.96, 1.50) Tertile 3: OR, 1.29 (1.02, 1.62) $P = 0.030$ No significance when those with past change in diet were excluded ($P = 0.098$ and $P = 0.149$, respectively) Data for other patterns not reported *Lp-PLA$_2$ activity (ng/mL^{1})* Male: Low-fat and high-fiber foods pattern: Tertile 2: OR, 0.92 (0.61, 1.38) Tertile 3: OR, 0.62 (0.40, 0.96) $P = 0.036$ No significance when those with past change in diet were excluded: $P = 0.352$ Milk-fat pattern Tertile 2: OR, 1.17 (0.85, 1.62) Tertile 3: OR, 1.50 (1.10, 2.05) $P = 0.011$ ***P = 0.009 when those with past change in diet were excluded*** Data for other patterns not reported

Abbreviations: AH, acetylhydrolase; BMI, body mass index; BMR, basal metabolic rate; CHD, coronary heart disease; circ., circumference; CVD, cardiovascular disease; DAC, dietary antioxidant capacity; DASH, Dietary Approach to Stop Hypertension; DBP, diastolic blood pressure; EC_{50}, half-maximal effective concentration; ELISA, enzyme-linked immunosorbent assay; EVOO, extra virgin olive oil; F, female; FA, fatty acid; FBG, fasting blood glucose; FRAP, ferric-reducing antioxidant power; HDL, high-density lipoprotein; IFG, impaired fasting glucose; iTRAQ, isobaric tags for relative and absolute quantitation; LDL-C, low-density lipoprotein cholesterol; Lp-PLA_2, lipoprotein-associated phospholipase A2; M, male; MPO, myeloperoxidase; MUFA, monounsaturated fatty acid; N/A, not applicable; OHA, oral hypoglycemic agent; OR, odds ratio; PAF, platelet activating factor; PBMC, peripheral blood mononuclear cells; PRP, platelet-rich plasma; PON1, serum paraoxonase and arylesterase 1; PUFA, polyunsaturated fatty acid; RCT, randomized controlled trial; SBP, systolic blood pressure; sdLDL, small dense low-density lipoprotein; SE, standard error; SF, saturated fat; SFA, saturated fatty acids; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TCA, trichloroacetic acid; TEAC, trolox-equivalent antioxidant power; TFA, trans fatty acids; TRAP, total radical-trapping antioxidant parameters; WHR, waist to hip ratio.

[a]Bold indicates statistically significant results $P \leq 0.05$. For some observational studies, only statistically significant results (or results approaching significance) are included, for brevity.

after 3 months.[82] In another RCT in which only cross-sectional data were extracted, Lp-PLA_2 activity was reported after a 12-week Dietary Approaches to Stop Hypertension diet run-in period before randomization.[87]

Three cohort studies examined posteriori dietary patterns. One study in Sweden used cluster analysis to identify 6 novel dietary patterns, and the authors reported somewhat inconsistent findings across male and female participants.[94] However, across both sexes, the low-fat and high-fiber dietary pattern (10.5% of total energy derived from fruit, 8% energy from low-fat milk, both high-fat and low-fat meats, and sweets) was associated with lower Lp-PLA_2 levels, whereas the milk-fat pattern (12% of total energy derived from a butter/rapeseed oil spread and other major energy sources that included cheese, whole milk, and, to a lesser extent, white bread and sweets) was associated with higher Lp-PLA_2 levels.[94] A second study in Greece also identified 6 unique dietary patterns and found a pattern rich in whole-wheat products with olive oil was inversely correlated with levels of lyso-PAF acetyltransferase (an enzyme related to PAF metabolism).[93] In the same study, a high dietary antioxidant capacity score (but not a Mediterranean diet score) was inversely associated with total PAF after adjustment for confounders.[93] The third study identified 3 unique dietary patterns: (1)a healthy dietary pattern (ie, high in fruits, dried fruit, olives, high- and low-fat dairy products, poultry and fish, liquid oils, and canned products), (2) semi-Mediterranean dietary pattern (ie, legumes, potatoes, eggs, red meats, tea, and coffee), and (3) a Western dietary pattern (dominated by carbonated drinks, fast foods, salty snacks, mayonnaise, and organ meats).[92] Compared with the healthy dietary pattern, the Western dietary pattern was associated with less favorable Lp-PLA_2 levels. After accounting for confounders, the semi-Mediterranean dietary pattern showed no effect on Lp-PLA_2 with the healthy dietary pattern as the referent.

Four novel biomarkers were identified in the literature as secondary outcomes for this review: serum paraoxonase and arylesterase 1 (PON1), myeloperoxidase (MPO), RANTES (chemokine ligand 5; regulated on activation, normal T-cell expressed and secreted), and LDL particle size. PON1 is a cardioprotective enzyme that prevents the accumulation of oxidized LDL and promotes cholesterol efflux out of macrophages.[97] MPO is an enzyme linked to inflammation and oxidative stress and has been shown to be involved in all stages of atherosclerosis.[98] RANTES is a pro-inflammatory cytokine that induces leukocyte activation and migration and is associated with a wide range of inflammatory disorders.[99] LDL particle size can be a marker used in the prediction of CVD. Small dense LDL particles are a distinct LDL subclass that is more pro-atherogenic than large LDL particles because they have a decreased affinity for the LDL receptor, resulting in longer circulation time; enter the arterial wall more easily; are more prone to entrapment in the arterial wall; and are more susceptible to oxidation.[100]

A vegetarian diet supplemented with peanuts (but not the same diet supplemented with coconut instead of peanuts) resulted in a significant increase in PON1.[83] Similarly, MPO was significantly increased in the peanuts-supplemented group but not the coconut group.[83] The largely vegetarian Pritikin dietary pattern showed no effect on PON1 levels.[90]

Similarly, a raw vegan dietary pattern intervention significantly lowered small dense LDL particles and decreased levels of MPO ($P = 0.056$).[89] A heart-healthy intervention resulted in no significant difference in RANTES in either the usual-care or intervention groups.[86] LDL particle size was significantly increased in the whole-grain dietary pattern interventions compared with a refined-grains dietary pattern.[84,85]

Risk-of-bias assessment identified 6 positive, 10 neutral, and 0 negative articles (Table 3). Studies that rated lower on the scale did so mostly because of inadequate description of follow-up methods and handling of withdrawals and methods of blinding. There were no discrepancies in outcome reporting when study reports were checked against the Clinical Trial Register of the International Clinical Trials Registry Platform of the World Health Organization.

DISCUSSION

In this systematic review, we investigated the association between overall dietary patterns and their effect on PAF and Lp-PLA_2 as novel biomarkers of inflammation. There was a small number of published dietary studies reporting these biomarkers. Thirteen of the 16 included studies reported Lp-PLA_2 and only 4 reported PAF, with 1 study reporting on both markers. The paucity of research in this area is likely due to the novelty of the markers, in addition to the difficulty in measuring them and a lack of an established reference range for PAF and Lp-PLA_2 activity in a normal, healthy population.

However, a key finding from this review is that a range of established dietary patterns broadly consistent with country-specific dietary guidelines around the world show promise in producing favorable changes in these novel biomarkers. These included Mediterranean dietary patterns, vegetarian dietary patterns, and other heart-healthy dietary patterns. Conversely, dietary patterns including foods that were more highly processed

Table 3 **Risk-of-bias assessment**

Reference	Relevance questions[a]				Validity questions[b]										Overall quality rating
	1	2	3	4	1	2	3	4	5	6	7	8	9	10	
Karantonis et al (2005)[88]															Neutral
Hernaez et al (2020)[81]															Positive
Makariou et al (2019)[82]															Positive
Shankar (2017)[83]															Neutral
Kim et al (2016)[84]															Neutral
Kim et al (2014)[85]															Positive
Wooten et al (2013)[86]															Positive
Rizos et al (2011)[87]															Positive
Antonopoulou et al (2006)[17]															Neutral
Najjar et al (2018)[89]															Neutral
Roberts et al (2006)[90]															Neutral
Richard et al (2014)[91]															Positive
Seyedi et al (2020)[92]															Neutral
Detopoulou et al (2013)[27]															Neutral
Hlebowicz et al (2011)[94]															Neutral
Chen et al (2011)[95]															Neutral

Green = Yes; Yellow = Unclear; Grey = N/A; Red = No

a Relevance questions (n = 4):
1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group?
2. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?
4. Is the intervention or procedure feasible?

b Validity questions (n = 10):
1. Was the research question clearly stated?
2. Was the selection of study subjects/patients free from bias?
3. Were study groups comparable?
4. Was method of handling withdrawals described?
5. Was blinding used to prevent introduction of bias?
6. Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?
7. Were outcomes clearly defined and the measurements valid and reliable?
8. Was the statistical analysis appropriate for the study design and type of outcome indicators?
9. Are conclusions supported by results with biases and limitations taken into consideration?
10. Is bias due to study's funding or sponsorship unlikely?

and reflective of Western diets were associated with unfavorable outcomes.

The finding that Mediterranean dietary patterns were associated with favorable changes in levels of both PAF and Lp-PLA_2 post intervention is unsurprising. The Mediterranean diet was associated with reduced risk of CVD, including a reduction in events and deaths in a recent systematic review, although the effect size was small and the quality of evidence low to moderate.[101] A previous systematic review that investigated the Mediterranean diet or its components and PAF and Lp-PLA_2 found a range of foods to have favorable effects; the authors concluded that dietary patterns that emphasize cereals, legumes, vegetables, fish, and wine were worthy of additional investigation.[30] This study also noted that research was lacking on olive oil (the most characteristic component of Mediterranean diets). Although not specific to these novel biomarkers, another systematic review found that a Mediterranean dietary pattern was associated with lower levels of other markers of inflammation and improved endothelial function.[102] A Mediterranean diet intervention also significantly improved dietary inflammatory index scores (a measure of potential of diet to affect established inflammatory cytokines) compared with a low-fat diet in people with coronary heart disease.[103]

People with cardiometabolic conditions or risk factors may have greater responses to dietary intervention. Results from 2 studies we included in the present review suggested that Mediterranean dietary patterns may have greater favorable effects on PAF-induced platelet activity in patients with type 2 diabetes who are treated with both medication and diet, compared with healthy control study participants.[17,88] It is possible that this was due to lower platelet resistance to PAF-induced platelet aggregation in participants with type 2 diabetes at baseline, compared with healthy participants, which provides greater scope for improvement because of their naturally higher levels of platelet hyperactivity resulting in increased activation and aggregation.[104]

Furthermore, the results of the present study demonstrated that vegetarian dietary patterns were associated with more favorable changes in levels of PAF and Lp-PLA_2. This is consistent with wider evidence supporting cardiovascular benefits of minimally processed plant-based diets, of which vegetarian dietary patterns are a subset.[105] Vegetarian diets emphasizing foods low in dietary fat may not confer the same benefits, because they are lower in fats that contain anti-inflammatory properties such as bioactive polar lipids (ie, phospholipids, sphingolipids, glycolipids) found in olive and seed oil, and higher-fat dairy products.[20] For example, in the Roberts study,[90] participants consumed non-fat milk that contained half the levels of PAF-inhibiting polar lipids than did whole milk.[106] Other research has highlighted potential benefits of full-fat dairy

consumption, due to a greater bioavailability of high-value nutrients such as vitamin D and other anti-inflammatory microconstituents.[107,108]

Within the current review, vegetarian diets with and without dairy and/or eggs were associated with favorable outcomes. One observational study found lower levels of Lp-PLA_2 in groups following a lacto-ovo vegetarian dietary pattern compared with groups who were omnivores; however, the former group had higher levels of high-sensitivity C-reactive protein than did the omnivore group.[95] These results are in contrast to those of a recent systematic review and meta-analysis that found vegetarian diets are associated with significantly lower levels of high-sensitivity C-reactive protein compared with nonvegetarian diets.[109] The researchers noted Taiwanese vegetarians consume fewer fresh vegetables, which they cook in oil, than do Western vegetarians, and they consume many deep-fried and refined soybean and grain products, which might contribute to higher high-sensitivity C-reactive protein levels.

The other heart-healthy dietary patterns associated with favorable effects on inflammation in this review are broadly similar to country-specific dietary guidelines across the United States, the United Kingdom, and Australia.[110–112] These guidelines advocate higher intakes of vegetables and fruits, moderate dairy consumption (albeit favoring reduced- or lower-fat options), plant-based oils, and unprocessed protein sources such as fish, lean meat, and legumes. A randomized dietary intervention study in healthy men and women compared a diet consistent with UK dietary guidelines with a representative UK diet and demonstrated a significant reduction in C-reactive protein levels after 12 weeks. This suggests that inflammation is positively affected when dietary guidelines are followed,[113] possibly via increased food sources of polyphenols,[114] known to be PAF inhibitors.[63] Research has shown an inverse association between Lp-PLA_2 and retinol and carotene, markers for provitamin A fruit and vegetable intake, in patients with incident CVD.[115] Higher intake of fruit and vegetables led to a reduction in levels of inflammatory biomarkers in a recent systematic review and meta-analysis.[116]

We found that a Western dietary pattern is associated with higher levels of inflammation. This is not unexpected, because Western dietary patterns are associated with increased risk of coronary heart disease in both men and women,[117,118] and given the known link between inflammation and heart disease. A recent review found that Western dietary patterns are associated with increased levels of the blood inflammatory biomarkers high-sensitivity C-reactive protein, leptin, and IL-6.[119]

Very few secondary outcomes were identified in this review; however, key markers appear to be PON1, MPO, and LDL particle size. Results for these outcomes were mixed. LDL particle size appears to be an important predictor of cardiovascular events and small dense LDL particles are more pro-atherogenic than large LDL particles.[100,120] Levels of Lp-PLA_2 in small dense LDL have been reported to be 5 to 10 times higher than in normal-size LDL.[121] Of the 3 secondary outcomes, PON1 may be a useful addition to future studies investigating PAF and Lp-PLA_2, given its presence within HDL and protective action against LDL oxidation.

Weight change may be a mediator of inflammatory biomarkers. Authors of a recent review (which did not include the novel biomarkers investigated in the present review) found no significant effect on markers of subclinical inflammation when examining whole foods and dietary patterns in weight-stable individuals with a high body mass index.[122] The review authors concluded that weight loss may be a key factor in dietary interventions that reduce inflammation. In the present review, there was no change in mean weight from baseline in 7 of 10 interventions, but there were improvements in inflammation after the interventions. Three studies noted significant weight loss, but inflammatory outcomes were inconsistent. One study[89] showed a weight loss of >6% of body weight after a 4-week intervention, with concomitant reductions in levels of novel inflammatory biomarkers. In contrast, the other 2 studies showed no or a worsening effect: one study[87] reported a small reduction in weight with no change in Lp-PLA_2 from baseline; the other study[90] reported a 3% reduction in body weight, but Lp-PLA_2 level actually increased after the intervention.

To our knowledge, this is the first systematic review to explore the association between dietary patterns, beyond the Mediterranean Diet, and the novel biomarkers PAF and Lp-PLA_2. Strengths of our study include a strong methodology and use of the PRISMA guidelines. A comprehensive literature search was performed using 4 databases. Screening of title and abstracts and full-text review for inclusion criteria were performed in duplicate. Data extraction was independently reviewed for accuracy and quality assessment was performed.

This review was comprehensive and systematic; however, the analysis is limited by the small number of studies adhering to the inclusion criteria assessing dietary patterns and these novel biomarkers. The sheer novelty of the markers of interest are another limitation, because measurement methods are varied and no consensus of cutoff points have been derived for either PAF or Lp-PLA_2 activity, making it difficult to interpret the results reported in the studies. Other limitations of this study include the wide diversity of groups reported in the studies, which makes it difficult to draw comparisons, and the inclusion of cross-sectional studies that encompass a high risk of bias and lower level of study

quality when compared with RCTs. The number of studies examining PAF was very limited, suggesting this is a gap in the literature. Large-scale intervention studies are needed to gain a better understanding of how diet affects this novel biomarker. Because little is known about the normal concentrations of both biomarkers in healthy populations, priority for research should be placed on establishing reference values to determine the clinical utility of these biomarkers.

CONCLUSION

There is limited evidence and considerable diversity in existing studies investigating dietary patterns and the novel inflammatory markers PAF and Lp-PLA_2. A range of well-established dietary patterns has potential to improve these novel markers, including Mediterranean, vegetarian, and other heart-healthy dietary patterns. Conversely, Western dietary patterns are associated with higher levels of inflammation, as measured by these markers. More, well-designed studies are needed to confirm these findings and identify other dietary patterns that could positively affect inflammation.

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Supporting Information

The following Supporting Information is available through the online version of this article at the publisher's website.

Table S1 Search terms used in the PubMed, CINAHL, Embase, and Cochrane databases

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